

**REMARKS**

First, it is noted that claims 10 and 18 are amended to more clearly delineate the distinction between the present invention and the cited art, i.e. that an oligonucleotide-camptothecin drug complex is provided which incorporates sufficient amounts of active lactone camptothecin drug to exert therapeutic activity when administered to the body, wherein at least a part of the camptothecin drug lactone ring is associated with the oligonucleotide and thereby protected from hydrolysis during administration, and wherein the camptothecin drug dissociates from the oligonucleotide within the body and exerts its therapeutic activities. As will be described in detail below, none of the art cited by the Examiner teaches nor fairly suggests these features. Support for the amendments is found throughout the Specification, for example at page 8, line 21 and continuing to page 9, line 8, Example 1 of the present application (pages 56-62), and original claim 9. Claim 11 is amended to correct a minor typographical error.

Turning to the substantive portions of the Office Action, the Examiner initially rejects claims 10, 15, 18, and 24 as non-enabled under 35 USC §112, 1<sup>st</sup> paragraph. The Examiner asserts that the Specification provides insufficient guidance as to the use of viral vectors to deliver the composition of the present invention absent undue experimentation.

The Examiner states that no indication is provided as to “how CPT which is a toxic drug can be stored stably in any viral vector to the extent that the intended use of

the viral vectors containing CPT/oligo complexes can be achieved so as to have a chemotherapeutic effect.” However, as specifically discussed in the Specification as filed (see page 2, line 16 and continuing to page 3, line 7) and as is well known in the art, it is the hydrolyzed or carboxylate form of camptothecin which is toxic. As noted numerous times in the Specification and claims of the present application, and as will be discussed in greater detail below, it is the lactone form of camptothecin, which exhibits reduced toxicity to cells, which is preserved in stable form in the camptothecin/oligonucleotide complexes of the present invention. As such the complexes, packaged for delivery in viral vectors, would not be in the toxic carboxylate form referred to by the Examiner. Accordingly, this reason for rejecting the claims under §112 1<sup>st</sup> paragraph cannot stand.

As to the Examiner’s concerns regarding the “undue experimentation” required to prepare the viral vectors of the present invention, the Applicants must respectfully point out that the accepted test under §112 1<sup>st</sup> paragraph is clearly met by the present application. A skilled artisan, in view of the knowledge available to one of skill in the art, must be able to make and use the claimed invention from the teachings provided without undue experimentation. Lack of actual examples teaching a skilled artisan to use the claimed system is simply not the law underlying the analysis of enablement. The test is not whether *in vivo* examples are provided, but rather whether undue experimentation

is required of a skilled artisan to take the teachings provided and make and use the invention. Indeed, the specification need not even include an example if the invention is otherwise disclosed in such a manner that one skilled in the art could practice it without an undue amount of experimentation.<sup>1</sup> As aptly stated by the Federal Circuit Court of Appeals, “[A] decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using *the knowledge available to such a person and the disclosure in the patent document*, could make and use the invention without undue experimentation . . .”<sup>2</sup> (emphasis added).

Thus, in passing on the issue of enablement it is critical to consider the knowledge available to the skilled artisan in the present art field, and the level of skill to be expected in an artisan in this field to determine what constitutes undue experimentation. The Examiner provides a reference summarizing the knowledge base expected of a skilled artisan in the field of delivery of DNA by viral vectors, but neglects to note that such delivery and methods for accomplishing same are known in the art, and indeed can be found in publically available laboratory manuals.

Accordingly, the skilled artisan in this field is clearly able to select from a variety of viral vectors and oligonucleotide sequences for packaging therein, with recognized

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<sup>1</sup> *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970).

<sup>2</sup> *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 15 USPQ2d 1321 (Fed. Cir. 1990).

and quantified properties, and to anticipate the expected results of incorporating one or more of the oligonucleotides into the vector of choice. Methods for packaging DNA in a viral vector such that the DNA expresses the desired protein (which, as summarized by the Examiner, requires a regulatory sequence operably linked to a coding sequence of a desired DNA) are well known in the art. The knowledge available to the skilled artisan in this field is therefore high. Even in the unpredictable arts, a disclosure of every operable species is not required.<sup>3</sup> Therefore, an exhaustive presentation of every specific step required for packaging the camptothecin/oligonucleotide complex of the present invention in a viral vector is unnecessary to satisfy the enablement requirement in the present case.

The art relevant to the present invention combines chemistry, molecular biology, and oncology, and the level of skill of an artisan in this field must be expected to be concomitantly high. Thus, the level of experimentation which may be necessary to practice the present invention, while arguably high, is not undue. It has been said that “[T]he test (of undue experimentation) is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine . . .”<sup>4</sup>

Regardless, each of the issues raised by the Examiner are faced by skilled artisans

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<sup>3</sup> Manual of Patent Examining Procedure §2164.03.

<sup>4</sup> *In re Wands*, 858 F.2d 731, 737, 8 USPQ 2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1970)).

in this field regardless of the viral vector and oligonucleotide used. As discussed previously, techniques for packaging a desired oligonucleotide in a viral vector for delivery and production of a desired protein are well known in the art. Examples of making the camptothecin/oligonucleotide complexes of the present invention are clearly provided. Techniques for delivering viral vectors containing the DNA of interest are also known to those skilled in the art, as noted in the Specification of the present application. The amount of experimentation required to deliver the complexes of the present invention via a viral vector, while perhaps extensive, is not undue in view of the above factors. Accordingly, the burden imposed by §112 1<sup>st</sup> paragraph is met for claims 10 and 18, and the claims are believed to be in condition for allowance. Claims 15 and 24 depending therefrom are believed to be in condition for allowance for the same reasons, and withdrawal of the rejection under §112 1<sup>st</sup> paragraph is respectfully requested.

Next, the Examiner rejects claims 18-21 under 35 U.S.C. §102(a) as anticipated by the J. Am. Chem. Soc. 120, 2979-2980. However, it is noted that this article is co-authored by the inventors of the present application, i.e. Yang and Burke (now deceased), and describes the present inventor's work. 35 U.S.C. §102(a) requires that an invention be described in a printed publication before the invention thereof by the applicant for patent, and since the publication describes the Applicant's work, this clearly

cannot be the case here. Accordingly, the rejection of claims 18-21 over the Yang et al. reference is respectfully submitted to be improper, and should be withdrawn.

The Examiner also rejects claims 18-21 over the Chourpa et al. reference, stating that Chourpa teaches that the hydrolysable alpha-hydroxy-lactone ring of any camptothecin used as a chemotherapeutic drug is essential for efficacy. This point is not in contention. The Examiner goes on to state that Chourpa teaches that CTPs-oligonucleotide complexes when prepared as a mixture promote complexation between CTPs and the oligonucleotides and stabilize the lactone form of CPT. Contrary to this position, Chourpa specifically teaches that in the absence of a topoisomerase I (topoI) cleavage site, there is no interaction between camptothecin and oligonucleotide. This is postulated by Chourpa because “[T]he data of the kinetic measurements show the ratio-dependent stabilisation of the lactone forms of CPTs in presence of an excess of olg1 or olg2 (with topoI cleavage site), but not of olg3 (without topoI cleavage site). The binding of camptothecins to the topoI cleavage site is known in the art, and indeed was referenced in the present application (see page 2, lines 9-15). Indeed, it is known that the lactone forms of camptothecins stabilize and form a reversible topoI-camptothecin-DNA ternary complex designated the cleavage complex, thereby preventing reforming of the DNA helix after the breakage/union cycle of the topoI reaction. Chourpa teaches nothing more than the specific kinetics of a mode of action for CPT which was already known in

the art.

In contrast, the present invention has surprisingly found that the lactone ring of camptothecin can be stabilized by binding to oligonucleotides, which is in no way taught or suggested by the specific binding site taught by Chourpa. Further, Chourpa neither teaches nor suggests the claimed combination of claim 18, i.e. a composition comprising an oligonucleotide-camptothecin drug complex wherein the camptothecin dissociates from the oligonucleotide within the body. There is no indication provided that the complexes of Chourpa will dissociate. As such, Chourpa does not teach the composition of claim 18 with the requisite specificity, and cannot form the basis for a §102 rejection.<sup>5</sup> Of course, in view of the tenet that claims depending from a properly allowable claim are also allowable, claims 19-21 are also believed to be patentable in view of the Chourpa reference.<sup>6</sup>

Turning next to the rejection of claims 9-13, 18-22, and 24-25 under 35 U.S.C. §103(a) over U.S. Patent No. 5,583,034 in view of either Yang et al. or Chourpa, further in view of Perez-Soler et al., the Examiner correctly characterizes the invention of Green (the ‘034 patent) as a mixture of an antisense nucleotide with a variety of compounds, including topoI inhibitors such as camptothecin (see Col. 8 of the ‘034 patent). The

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<sup>5</sup> *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 2 USPQ2d 1051 (Fed. Cir. 1987).

<sup>6</sup> *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Examiner states correctly also that the Green patent does not teach that lactone forms must be present in a camptothecin for efficacy, or that the antisense nucleotides must be complexed to the pharmaceutical composition.

The Examiner supports the rejection by stating that when Yang et al., Chourpa, and Perez-Soler are considered along with Green, motivation is provided to formulate a camptothecin-oligonucleotide complex wherein the lactone form of camptothecin is preserved, and to encapsulate the complex in a liposome. It must respectfully be pointed out that it is the complex formed between camptothecin and oligonucleotide to preserve the stability of the lactone form which provides the inventive step of the present invention. As discussed above, Yang et al. cannot properly be used as a reference against the present invention, being the inventor's own work. Chourpa and others require a specific binding site (the GC base pair topoI cleavage site) for binding of camptothecin and oligonucleotide, and indeed teach that in the absence of this site there is no binding and stabilization of the lactone ring (i.e. the olg3 example of Chourpa). The Examiner states that [I]t would have been obvious to one of ordinary skill in the art that the affinity between CPTs and antisense oligonucleotides so as to form a complex of CPTs and oligos is the intrinsic property of the CPTs when put in contact with oligonucleotides..." If that is the case, why was there no binding and stabilizing effect on the lactone ring in Chourpa when attempting to bind camptothecin to olg3?

In total contrast, no specific base pair site is required for complexation and stabilization of the lactone ring by oligonucleotides in the present invention. Green does not teach formation of a complex, and further provides no indication of any method for stabilizing the lactone form, or any motivation to do so. Perez-Soler teaches only incorporation of camptothecin into liposomes, which was already known in the art and therefore adds nothing to the present analysis of camptothecin-oligonucleotide complexes.

It is a settled point of law that a reference or combination of references, in order to provide a basis for an “obviousness” rejection, must provide some teaching, suggestion, or motivation to one of skill in the art to modify the reference to arrive at the claimed invention. In the absence of such suggestion or motivation, the *prima facie* case of obviousness is defective.<sup>7</sup> As has already been noted above, the Green patent specifically teaches a mixture, and provides no motivation for (or suggestion of the need for) forming a camptothecin-oligonucleotide complex, or for otherwise preserving the lactone form of camptothecin *in vivo* in the Green mixture. Yang et al. cannot be relied on for a rejection of any claims, being the present inventor’s own work. Chourpa teaches away from forming a complex of camptothecin and an oligonucleotide to stabilize the lactone form of camptothecin, absent a topoI cleavage site. Perez-Soler teaches use of a liposome to

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<sup>7</sup> *In re Geiger*, 815 F.2d 686, 2 USPQ 2d 1276 (Fed. Cir. 1987); *In re Kotzab*, 217 F. 3d 1265, 55 USPQ 2d 1313 (Fed. Cir. 2000).

protect the lactone form of camptothecin, which would render unnecessary the complex of the present invention. In view of these points, it is respectfully suggested that the cited art provides no teaching, suggestion, or motivation to arrive at the claimed combinations of claims 9, 10, and 18, and the rejections should be withdrawn. This being the case, the claims depending therefrom are also necessarily in condition for allowance.<sup>8</sup>

Next, the Examiner rejects claims 10, 14, 18, and 22 under 35 U.S.C. §103(a) over the Green patent with either Yang et al. or Chourpa, further in view of Matteucci. The reasons that Green, Yang, and Chourpa cannot serve as a basis for rejection of any of the claims of the present invention on the grounds of obviousness have been described in detail above. The Examiner cites Matteucci for the proposition that triple helix forming oligonucleotides can be conjugated to camptothecins to render them sequence specific “with respect to the activity of CPTs.” With respect, while accurate as to the teachings of Matteucci, this characterization simply is not relevant to the present invention. The present invention claims a camptothecin-oligonucleotide complex formulated whereby the active (lactone) form of camptothecin is protected and stabilized by the complex for later release in the body. Matteucci simply does not teach this, but merely provides a method for targeting a topol I lesion to a site specific sequence on DNA using a specific type of oligonucleotide, i.e. triple helix forming. There is no indication

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<sup>8</sup> *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

that any other type of oligonucleotide is considered, nor is any motivation provided to complex any other type of oligonucleotide to a camptothecin. This is because the triple helix forming oligonucleotide is essential to the purpose of Matteucci. Still further, there is no motivation to provide an oligonucleotide-camptothecin drug complex which may be utilized in a chemotherapeutic composition, much less that the camptothecin drug is reversibly bound to the oligonucleotide whereby it may be metabolically released from the oligonucleotide within the body as claimed in the present application. There being no motivation or suggestion provided to combine the cited references to arrive at the claimed combinations of the present invention, it is respectfully requested that the rejection of claims 10 and 18 be withdrawn. Of course, in accordance with *In re Fine*, the respective dependent claims (14 and 22) are also in condition for allowance.

Finally, claims 18 and 22 are rejected under 35 U.S.C. §103(a) over Chourpa in view of Matteucci. As noted above, Chourpa specifically teaches a site-specific binding between camptothecin and DNA, i.e. the GC base pairs at the topoI cleavage site. Similarly, Matteucci teaches a method of complexing triple helix forming (and no other) oligonucleotides to camptothecin to create a sequence-specific trapping of a cleavable complex whereby a topoI lesion may be targeted to a precise site. A bonding of camptothecins and an oligonucleotide under conditions which promotes stability of the lactone form of the drug but allows release of the drug in the body is simply neither

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taught nor suggested. Accordingly, the rejection of claim 18 (and therefore of claim 22 depending therefrom) is improper and withdrawal thereof is respectfully requested.

It is now believed that the present application is in condition for allowance.

Accordingly, allowance of all claims of the application is respectfully requested. If any issues remain, however, the Examiner is respectfully requested to contact the Applicants' attorney at the telephone number of record in order to expedite the prosecution of this patent application.

Respectfully submitted,

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